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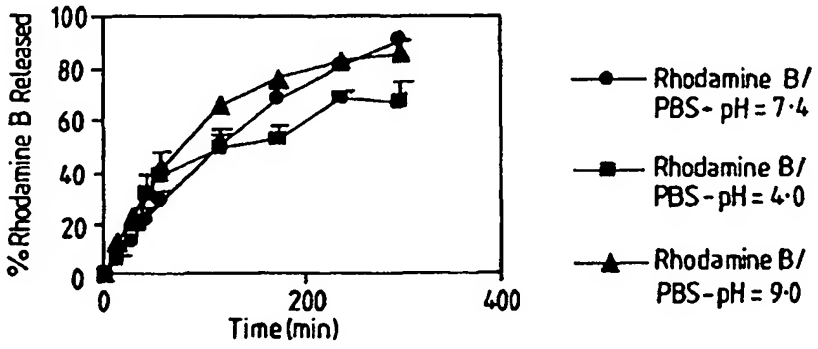

(57) Abstract

The present invention is directed to an erodible solid hydrogel material for delivery of biologically active agents such as pharmaceuticals. Said solid hydrogel material is formed from non–covalently cross–linked polysaccharide derivatives, which bear both hydrophilic and hydrophobic groups. Gel formation is then induced for example by freeze–drying. The gel is erodible either by simple mechanical disruption of the gel or due to biological processes acting on the hydrogel.

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ERODIBLE SOLID HYDROGELS FOR DELIVERY OF BIOLOGICALLY ACTIVE MATERIALS

The present invention relates to hydrogels formed from polysaccharide derivatives which are suitable for delivery of biologically active agents. A hydrophilic polysaccharide derivative is hydrophobised to form a derivative bearing at least one long chain acyl residue. Gel formation is induced for example by freeze-drying and the gel loaded with a biologically active agent.

Hydrogels for drug delivery have been previously described. GB 2047093 for example discloses a controlled release composition which comprises a pharmaceutically active agent associated with a polymeric carrier. The polymeric carrier comprises residues which are cross-linked through urethane groups and are based on polyethylene oxide. The polymeric carrier is a crystalline hydrogel in the dry form and swells in an aqueous medium. However, the hydrogels are designed to be insoluble and non-erodible. If administered to a person this has the disadvantage that once the biologically active agent has been delivered, the spent hydrogel material must be removed in order to prevent the formation of fibroids or otherwise excreted from the body.

It is therefore amongst the objects of the present invention to provide a hydrogel which is erodible in situ.

The present invention provides an erodible solid hydrogel material comprising non-covalently cross-linked polysaccharide derivatives, having both hydrophilic and hydrophobic portions.

In a preferred aspect the present invention provides a delivery device comprising an erodible solid hydrogel material comprising non-covalently cross-linked polysaccharide derivatives having both hydrophilic and hydrophobic portions in association with a biologically active agent, particularly a pharmaceutically active agent.

The term "hydrogel" as used herein is understood to mean a material which becomes hydrated and swells when placed in an aqueous medium. The hydrogel is erodible in the sense that it breaks down naturally over time, either by simple mechanical disruption of the hydrogel, or alternatively due to biological processes acting on the hydrogel. In any case the hydrogel is preferably substantially eroded once *in situ* within about 2 to 14 days.

The hydrogel material comprises non-covalently cross-linked polysaccharide derivatives having both hydrophilic and hydrophobic portions which, without being bound by any particular theory, are thought to associate to form the solid hydrogel material due to the interaction of the hydrophobic groups present on the polysaccharide derivative.

The polysaccharide derivative is preferably a derivative of chitosan, pullulan or dextran and most preferably comprises 1,4-linked saccharide units. Normally, substitution by the hydrophilic moiety occurs at the C6 position of a saccharide unit.

The hydrophobic group is preferably joined to a saccharide unit by an amide, ester, ether or amine linkage,

most preferably by an amide linkage. In a further preferred embodiment, this group is substituted at the C2 position in a 1,4-linked saccharide unit.

The hydrophilic group may be non-ionic and is preferably a group of the formula R^1, wherein R^1 is selected from mono- and oligo-hydroxy C_{1-6} alkyl, mono- and oligo-hydroxy substituted C_{2-6} acyl, C_{1-2} alkoxy alkyl optionally having one or more hydroxy groups substituted on the alkoxy or alkylene groups, and C_{1-4} alkyl (oligo- or poly-oxa C_{1-3} alkylene) optionally hydroxy substituted preferably oligo- or polyglycerol ethers such as those described in GB-A-1,529,625, for example containing up to 10 glycerol units; and wherein R^1 is joined via an ether linkage to a saccharide unit of the polysaccharide.

It is to be understood herein that the term acyl includes alkenoyl and alkynoyl groups as well as alkanoyl groups.

The hydrophobic group is preferably a C_{12-24} alkyl, alkenyl, alkynyl or acyl residue.

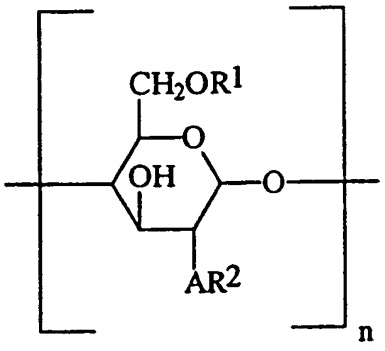
Said polysaccharide derivatives have a degree of substitution by hydrophilic groups in the range 0.01 - 2 substituents per monosaccharide unit, preferably greater than 0.01 and most preferably 1 per saccharide unit.

The ratio of hydrophilic:hydrophobic groups in the compounds of this invention is in the range 10:1 to 0.1:1, preferably between 5:1 and 1:1 more preferably 3:1 and 1.3:1 it is possible through experimentation to control the ratio of hydrophilic: hydrophobic groups for any particular

use. In this manner the swellability of any particular hydrogel may be controlled as well as the release properties of the hydrogel. It may also be possible to control the erodibility of the hydrogel in this manner.

A preferred range of polysaccharide derivatives for use in the present invention are the N-substituted derivatives of poly-amino glycans most preferably N-acyl glycol chitosans, especially N-palmitoyl glycol chitosan (poly[β(1→4)-2-deoxy-2-hexadecanamido-6-O-(2-hydroxyethyl)-D-glucopyranose]. In this case, the presence of free amino groups is advantageous from a point of view of permitting complexing or conjugation with for example drug molecules or dissolved ions.

In a preferred embodiment, said polysaccharide derivatives have the formula:



wherein each R^1 is selected from hydrogen, mono- and oligo-hydroxy C_{1-6} alkyl, mono- and oligo-hydroxy substituted C_{2-6} acyl, C_{1-2} alkoxy alkyl optionally having one or more hydroxy groups substituted on the alkoxy or alkylene groups, C_{1-4} alkyl (oligo- or poly-oxa C_{1-3} alkylene) optionally hydroxy substituted such as polyglycerol ethers, for example

containing up to 10 glycerol units, provided that at least one of the groups R^1 is other than hydrogen;

A is -NH-, or -O-;

each R^2 is selected from hydrogen, C_{12-24} alkyl, alkanoyl, -alkenyl, alkenoyl, -alkynyl or alkynoyl or acyl provided that at least one of the groups R^2 is other than hydrogen; and

n is 5-2000.

Preferably, the group R^1 has the formula $-CH_2CH_2OH$ or $-CH_2CH(OH)CH_2OH$, R^2 is C_{16-18} acyl and A is -NH-.

The compounds may be formed according to any of the standard techniques described in the prior art for the derivatisation of polysaccharides (see for example, Yoshioka et al Biosci. Biotech. Biochem., 1993, 57, 1053 - 1057 and Biosci. Biotech. Biochem. 1995, 59, 1901 - 1904). The technique may involve derivatisation of a polysaccharide starting material by a hydrophilic group in a first step, followed by a second step comprising attachment of a hydrophobic group or vice-versa. Alternatively, commercially-available polysaccharide derivatives already possessing a hydrophilic group may be hydrophobised using standard techniques to form a polysaccharide derivative according to this invention.

Solid hydrogel formation may be induced by freeze-drying a solution comprising the polysaccharide derivatives.

Preferably the biologically active agent is added to the solution prior to freeze-drying and therefore the

biologically active agent becomes associated with the freeze-dried solid hydrogel material. The biologically active agent only becomes released from the hydrogel upon rehydration and swelling of the hydrogel material.

Apart from controlling the ratio of hydrophilic: hydrophobic groups, swelling, irritability and/or release of the biologically active agent may be controlled by modifying the hydrogel components. For example salts such as sodium chloride, may be added to the hydrogel in order to modify release of the biological agent for the hydrogel and/or stabilise the hydrogel such that it erodes more slowly. Alternatively preparing the drug loaded hydrogel in the presence of phosphate buffered saline pH=7.4 (PBS) may be used to control the release.

Examples of classes of biologically active substances which may be incorporated in the hydrogels of the present invention include pharmaceuticals, bacteriostats, viruscides, insecticides, herbicides, larvicides, fungicides, algaecides, nematocides, topical or dermatological agents, antifoulants, for marine growth prevention, enzymes and preservatives. Of particular interest are hydrogels of the present invention comprising, as a biologically active substance, at least one pharmaceutical.

The compositions of this invention thus find wide application in medical and surgical, including veterinary, contexts and in horticulture and agriculture as well as outside these areas.

Specific classes of pharmaceuticals which may be utilised include abortifacients, hypnotics, sedatives, tranquilisers, anti-pyretics, anti-inflammatory agents, anti-histamines, anti-tussives, anticonvulsants, muscle relaxants, anti-tumour agents, for example those for the treatment of malignant neoplasia, local anaesthetics, anti-Parkinson agents, topical or dermatological agents, diuretics, for example those containing potassium, such as potassium iodide, preparations, for the treatment of mental illness, for example preparations containing lithium for use in the treatment of manic depression, anti-spasmodics, anti-ulcer agents, preparations containing various substances for the treatment of infection by pathogens including anti-fungal agents, for example metronidazole, anti-parasitic agents and other anti-microbials, anti-malarials, cardiovascular agents, preparations containing hormones, for example androgenic, estrogenic and progestational hormones, notably steroids such as oestradiol, sympathomimetic agents, hypoglycaemic agents, contraceptives, nutritional agents, preparations containing enzymes of various types of activity, for example chymotrypsin, preparations containing analgesics, for example aspirin, and agents with many other types of action including nematocides and other agents of veterinary application. Mixtures of active substances may be incorporated into the hydrogel.

The hydrogels may be used as film or powder but are most preferably used in the form of a shaped body such as

a hollow or blank cylinder, a sphere, a tablet or a slab and the nature of the shape and its dimensions may be selected appropriately. Preferably controlled release of the biologically active agent occurs over an appropriate time period and conveniently of a major proportion, for example 80% or 90% by weight of the active substance is released over this time. Initial release at a substantially constant rate, i.e. approximating to linear release, is an appropriate target in certain instances. Preferably the biologically active agent is released over a period in the range 1h - 14 days more preferably 12-24 hours.

Certain of the areas of pharmaceutical utility for hydrogels according to the present invention, such as the administration of hormones, drugs for the treatment of prophylaxis of various conditions, e.g. substances having activity against pathogenic micro-organisms, are particularly suited to vaginal or rectal administration of the active substance and pessaries are of especial interest in such contexts. The compositions may, however, be used for various localised application in other parts of the body such as the treatment of maladies of the mouth or eye, for example glaucoma. The compositions are also of interest for oral administration or in a topical patch to release a drug which can treat or be absorbed by the skin; and for use by implantation.

In this respect it has been observed that hydrogels of the present invention may display different release

properties in response to the surrounding pH. For example the hydrogel material may retard release of the active agent when placed in acidic pH. This observation may be of particular importance when designing hydrogels according to the present invention for oral administration. Due to the variation in pH occurring throughout the alimentary canal it may be possible to formulate hydrogels which release the majority of their active substance in one particular area of the alimentary canal.

The present invention will now be described further by the following non-limiting examples, wherein,

Figure 1 is a graph showing the percentage swelling ratio (swollen weight/dry weight) against time for a hydrogel of the present invention when placed in water;

Figure 2 is a graph showing the percentage swelling ratio against time for the hydrogel in various aqueous media;

Figure 3 is a graph showing the percentage swelling ratio of the hydrogel when placed in water and salt solutions of varying concentration.

Figure 4 is a graph showing the release of a model drug (ie. Rhodamine B) from the hydrogel material, when placed in water of varying pH;

Figure 5 is a graph showing the release of a model drug (ie. Rhodamine B) from the hydrogel material when placed in PBS of varying pH; and

Figures 6a - 6c are graphs showing the comparison between the results displayed in Figures 4 and 5.

Example 1 - Preparation of glycol chitosan based hydrogel (initial 1:1 ratio of glycol chitosan: palmitoyl units)

250mg glycol chitosan was dissolved in 40ml water containing 190mg sodium bicarbonate, 25ml of absolute ethanol was then added.

Separately, 396mg palmitic acid N-hydroxysuccinimide was dissolved in 300ml absolute ethanol. This ethanolic solution was placed in a separatory funnel and added dropwise, with continuous stirring, to the alkaline solution of glycol chitosan over a period of one hour.

The resulting mixture was left stirring for 72 hours, protected from light.

At the end of this period 50ml acetone was added and the reaction mixture evaporated under reduced pressure at 45°C to remove the ethanol and acetone and reduce the volume to approximately 50ml (nb not to dryness). The aqueous dispersion was then extracted 3 times with diethyl ether (100ml) and left to stand in a fume cupboard for 2h to allow all residual ether to evaporate.

The aqueous mixture was then dialysed against 5L water for 34h with 6 changes of dialysate: after 1h, 3h, 5h, 7h, 24h and 30h. At the end of this period the contents of the dialysis bag were transferred to a polypropylene container and frozen overnight.

The frozen product was then placed in a freeze drier for 72h or until dry.

The substitued glycol chitosan so produced conforms to formula I (data not shown). By way of support characterisation details of a similar substituted glycol chitosan (initial 4:1 ratio of glycol chitosan: palmitoyl units) are presented below.

Characterisation of GCP41 (initial 4:1 ratio of glycol chitosan: palmitoyl units)

^1H NMR.

Glycol chitosan is moderately soluble in water (2mg mL^{-1}) and ^1H NMR (with integration) and ^1H - ^1H COSY experiments were carried out on glycol chitosan in (D_2O, Sigma Chemical Co., UK) and GCP41 in a CD_3OD/D_2O mixture using a Bruker AMZ 400MHz in order to assign the non-exchangeable coupled protons.

FT-IR.

FT-IR was performed in potassium bromide discs on a Mattson Galaxy FT-IR.

The level of hydrophobic modification in GCP41 and the original level of acetylation in glycol chitosan were assessed by ^1H NMR (Vårum et al 1991, Yoshioka et al 1993). In this way the batch of glycol chitosan (Sigma Chemical Co, UK - 105H0111) that was used was found to be one third acetylated. Proton assignments,
δ0.86p.p.m = CH_3 (palmitoyl) δ1.25p.p.m = CH_2 (palmitoyl), δ1.89p.p.m = CH_2 (palmitoyl - shielded by carbonyl),

δ2.13p.p.m = CH_3 (acetyl - GCP41), δ2.14p.p.m. = CH_2 (adjacent to carbonyl protons), δ1.99p.p.m = CH_3 (acetyl - glycol chitosan), δ2.71p.p.m = CH (C2 sugar proton - GCP41), δ2.64p.p.m = CH (C2 sugar proton - glycol chitosan), δ3.31p.p.m = methanol protons, δ3.3 - 4.0p.p.m = non-exchangeable sugar protons, δ4.4p.p.m = water protons. The level of hydrophobic modification in GCP41 was assessed by using the ratio of non-exchangeable C2 protons to methyl protons (spectrum b) and was found to be 14.48 ± 2.88% (mean ± s.d., n = 3) with values lying between 11 and 16 mole %. The ratio of N-acetyl protons, C2 sugar protons, 9 additional sugar/glycol non-exchangeable protons remains at (~1:1:10) in both spectra.

GCP41 was insoluble yet dispersible in D_2O to give a cloudy liquid which remained without a sediment for at least 4 weeks. The ^1H NMR spectra of a fresh sample of this dispersion is devoid of signals for the fatty acid side chain protons. This suggests that palmitoyl glycol chitosan in water adopts an orientation in which the fatty acid side chains exist in hydrophobic domains separated from the hydrophilic part of the polymer. The acetyl group appears to be an integral part of the hydrophilic portion of the molecule in the modified polymer as signals for the acetyl groups are clearly seen in the GCP41 - D_2O spectra. Hence there was no co-operative association between the acetyl group and the hydrophobic side chains when palmitoyl glycol chitosan was dispersed in water. Freeze fracture electron microscopy did not reveal the existence of any

discernible particulate matter in this cloudy liquid.

The GCP41 FT - IR spectrum revealed a sharpening of the amide peak at 1648 cm^{-1}. The starting material glycol chitosan contains a relatively smaller amide peak at 1653 cm^{-1}.

Example 2 - Swelling of the hydrogel material in various liquid media

Pieces of the freeze-dried material prepared according to Example 1 were placed in 25ml portions of various media (ie. water, 0.08M sodium tetraborate, NaCl and phosphate buffered saline (PBS)).

The pieces were removed at regular intervals and weighed to determine the degree of "water" uptake. The results are shown in Figures 1 - 3. It can be observed that in PBS at approximately neutral (ie. physiological) pH or acid pH swelling of the gel was retarded in comparison with water alone, sodium tetraborate (0.08M) or alkali PBS. Additionally it can be seen that the addition of salt caused the retardation of swelling. It was also observed (not shown) that at the highest concentration of salt there was a greater absorbance of water with time and that the gel took longer to disintegrate. If handled the gel disintegrates within 5 hours but if left undisturbed this takes longer.

Example 3 - Release of Rhodamine B from the hydrogel

Hydrogel material was prepared according to Example 1. However, immediately after dialysis, before freeze-drying the gel was loaded with 0.05mM Rhodamine B in PBS (pH 4.0, 7.4 and 9.0). Approximately 0.25ml of Rhodamine B was added per 1ml of the gel/solution. The gel was then freeze-dried as before.

In order to determine the rate of release of the Rhodamine B from the gel, pieces were placed in dialysis tubing along with 1ml PBS of the appropriate pH. The tubing was then placed in 70ml PBS of the same pH in a waterbath at 35°C. 1ml aliquots were removed after specific time intervals (and replaced with fresh PBS) over a 5hr period. The samples were then assayed for Rhodamine B by fluorimetry. The results are shown in Figures 4 and 5. It can be seen that Rhodamine B was gradually released over a five hour period. Acidic pH also tended to retard the release of Rhodamine B.

It can also be seen that from Figures 6a - 6c that Rhodamine B release was less in PBS in comparison to water.

CLAIMS

1. An erodible solid hydrogel material comprising non-covalently cross-linked polysaccharide derivatives, having both hydrophilic and hydrophobic portions.

2. The erodible solid hydrogel material according to claim 1 associated with a biologically active agent.

3. The erodible solid hydrogel material according to either of claims 1 or 2 formed through association of polysaccharide derivatives due to interaction of hydrophobic groups present on the said polysaccharide.

4. The erodible solid hydrogel material according to any preceding claim wherein said polysaccharide comprises 1,4-linked saccharide units.

5. The erodible solid hydrogel material according to any preceding claim wherein said polysaccharide is a derivative of chitosan, pullulan or dextran.

6. The erodible solid hydrogel material according to any preceding claim wherein the hydrophobic group is joined to a saccharide unit by an amide, ester, ether or amine linkage.

7. The erodible solid hydrogel material according to any preceding claim wherein the hydrophobic group is substituted at the C2 position in a 1,4-linked saccharide unit.

8. The erodible solid hydrogel material according to any preceding claim wherein substitution by the hydrophilic moiety occurs at the C6 position of a saccharide unit.

9. The erodible solid hydrogel material according to any preceding claim wherein the hydrophilic group is a non-ionic group R^1, where R^1 is selected from mono- and oligo-hydroxy C_{1-6} alkyl, mono- and oligo-hydroxy substituted C_{2-6} acyl, C_{1-2} alkoxy alkyl optionally having one or more hydroxy groups substituted on the alkoxy or alkylene groups, and C_{1-4} alkyl (oligo- or poly-oxa C_{1-3} alkylene) optionally hydroxy substituted preferably oilgo- or polyglycerol ethers; and wherein R^1 is joined via an ether linkage to a saccharide unit of the polysaccharide.

10. The erodible solid hydrogel material according to any preceding claim wherein the hydrophobic group is a C_{12-24} alkyl, alkenyl, alkynyl or acyl residue.

11. The erodible solid hydrogel material according to any preceding claim wherein the degree of substitution by hydrophilic groups is 0.01 - 2 substituents per monosaccharide unit.

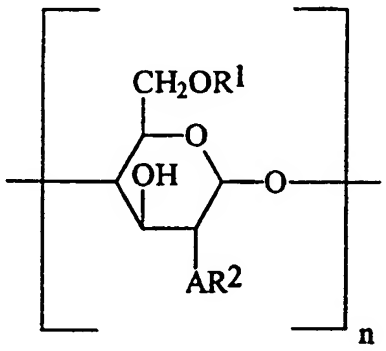
12. The erodible solid hydrogel according to any preceding claim wherein the ratio of hydrophilic : hydrophobic groups is in the range 10:1 to 0.1:1.

13. The erodible solid hydrogel according to any preceding claim wherein said polysaccharide derivative is an N-substituted derivative of a poly-amino glycan.

14. The erodible solid hydrogel material according to claim 13 wherein said polysaccharide derivative is an N-acyl glycol chitosan.

15. An erodible solid hydrogel material according to claim 14 wherein said polysaccharide derivative is N-palmitoyl glycol chitosan (poly[β(1-4)-2-deoxy-2-hexadecanamido-6-O-(2-hydroxyethyl)-D-glycopyranose]).

16. An erodible solid hydrogel material according to any one of claims 1 - 12 wherein said polysaccharide derivatives have the formula:



wherein each R^1 is selected from hydrogen, mono- and oligo-hydroxy C_{1-6} alkyl, mono- and oligo-hydroxy substituted C_{2-6} acyl, C_{1-2} alkoxy alkyl optionally having one or more hydroxy groups substituted on the alkoxy or alkylene groups, C_{1-4} alkyl (oligo- or poly-oxa C_{1-3} alkylene) optionally hydroxy substituted such as polyglycerol ethers, for example containing up to 10 glycerol units, provided that at least one of the groups R^1 is other than hydrogen;

A is -NH-, or -O-;

R^2 is selected from hydrogen, C_{12-24} alkyl, -alkanoyl, -alkenyl, -alkenoyl, -alkynyl or alkynoyl or acyl, provided that at least one of the groups R^2 is other than hydrogen; and n is 5-2000.

17. An erodible solid hydrogel material according to claim 16 wherein R^1 has the formula $-CH_2CH_2OH$ or $-CH_2CH(OH)CH_2OH$, R^2 is C_{16-18} acyl and A is -NH-.

18. A delivery device comprising the erodible solid hydrogel material according to any preceding claim for delivery of a biologically active agent.

19. A delivery device comprising an erodible solid hydrogel material comprising non-covalently cross-linked polysaccharide derivatives having both hydrophilic and hydrophobic portions in association with a biologically active agent.

20. The erodible solid hydrogel material or a delivery device according to any preceding claim wherein formation of said erodible solid hydrogel material is induced by freeze-drying a solution comprising the polysaccharide derivatives.

21. A delivery device according to claim 20 comprising said erodible solid hydrogel material associated with a biologically active agent wherein the agent is added prior to freeze-drying.

22. A delivery device according to any one of claims 18 - 21 wherein said biologically active agent is released from said hydrogel upon rehydration and swelling of said hydrogel material.

23. A delivery device according to any one of claims 18 - 22 wherein the swelling, irritability and/or release of said biologically active agent may be controlled by the ratio of hydrophilic : hydrophobic groups.

24. A delivery device according to any one of claims 18 - 23 further comprising salts.

25. A delivery device according to any one of claims 18 - 24 wherein said hydrogel is prepared in the presence of phosphate buffered saline pH=7.4(PBS).

26. A delivery device according to any one of claims 18 - 25 wherein the biologically active agent is a pharmaceutical, bacteriostat, viruscide, insecticide, herbicide, larvicide, fungicide, algaecide, nematocide, topical or dermatological agent, antifoulant, enzyme or preservative.

27. Use of an erodible solid hydrogel material according to any one of claims 1 to 17 in the manufacture of a composition for use in therapy.

28. Use of an erodible solid hydrogel material according to any one of claims 1 to 17 in the manufacture of a composition for use in horticulture or agriculture.

29. The erodible solid hydrogel material according to any one of claims 1 - 17 formed as film or powder.

30. The erodible solid hydrogel material according to claim 29 wherein the film or powder is in the form of a shaped body.

31. The erodible solid hydrogel material according to claim 30 wherein the shaped body is a hollow or blank cylinder, a sphere, a tablet or a slab.

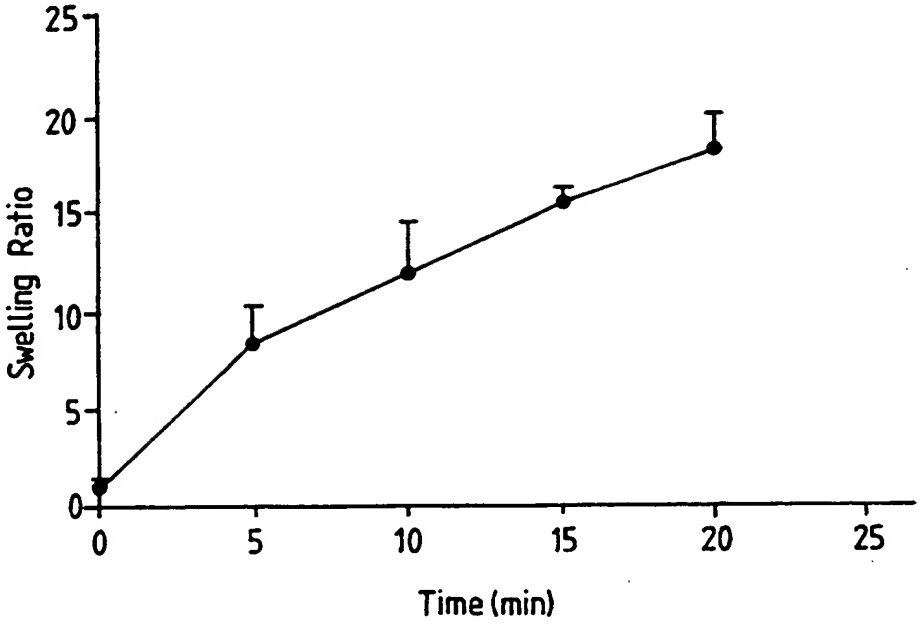

Swelling Ratio
25
20
15
10
5
0
0
5
10
15
20
25
Time (min)

Fig. 1

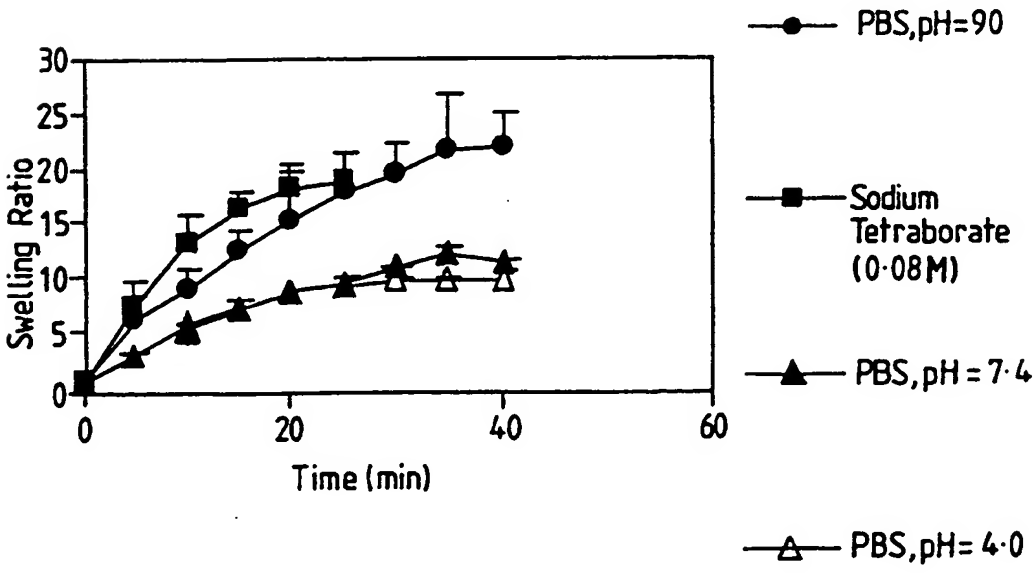

Swelling Ratio
30
25
20
15
10
5
0
0
20
40
60
Time (min)
PBS,pH=90
Sodium Tetraborate (0·08M)
PBS,pH=7·4
PBS,pH=4·0

Fig. 2

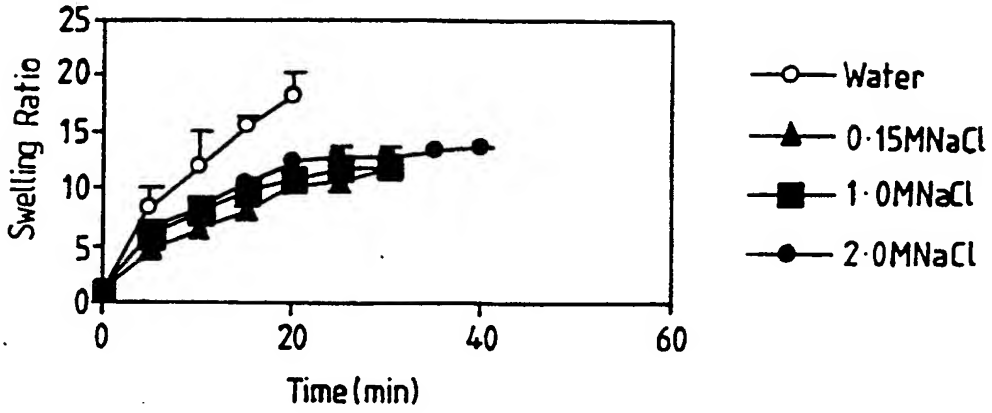


Fig. 3

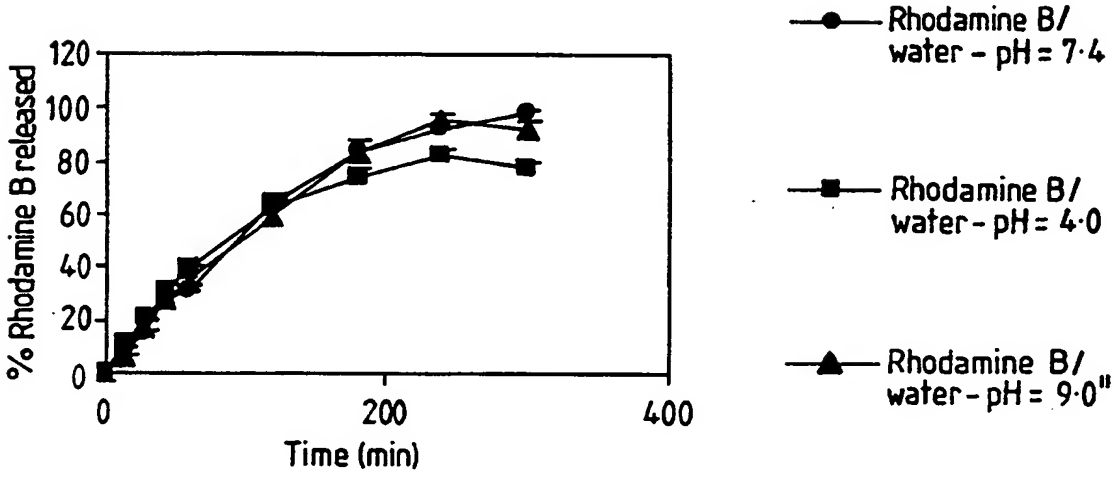


Fig. 4

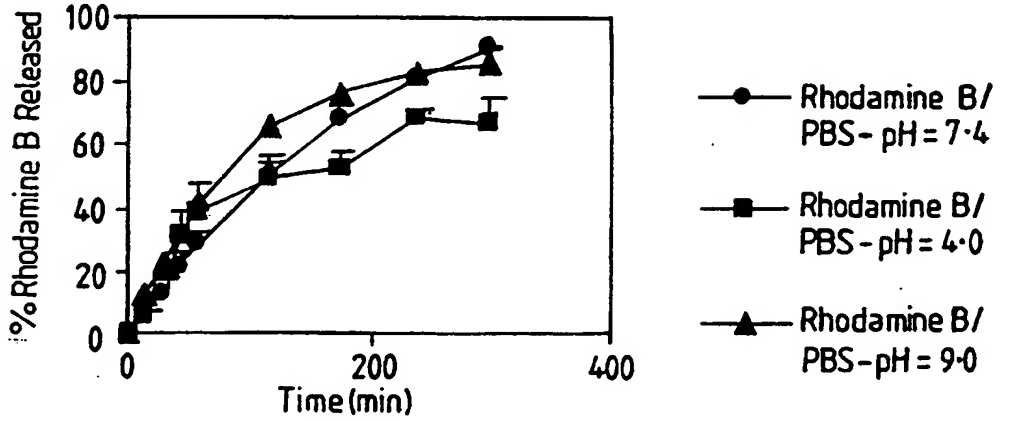


Fig. 5

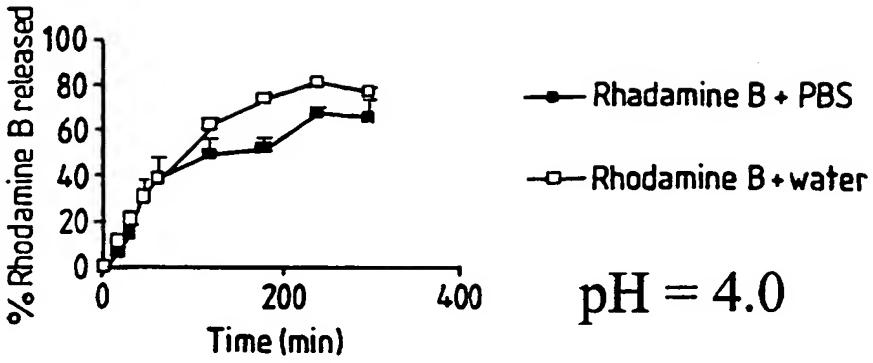


Fig. 6a

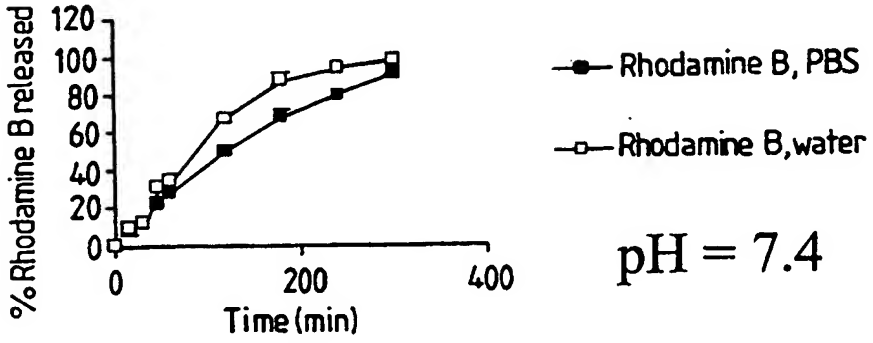


Fig. 6b

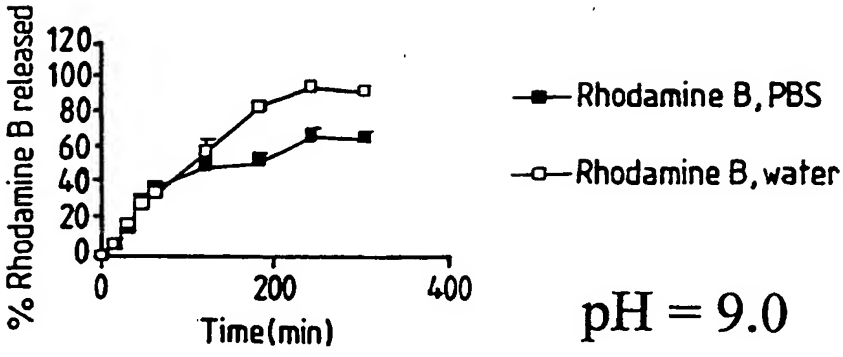


Fig. 6c

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 99/02960

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08L5/08 A61K9/16 A61K9/20 C08J3/075

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C08J C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 7, no. 225 (C-189), 6 October 1983 (1983-10-06) & JP 58 118801 A (ASAHI KASEI KOGYO KK), 15 July 1983 (1983-07-15) abstract & DATABASE WPI Week 198334 Derwent Publications Ltd., London, GB; AN 743795 ---	1,4-12
Y	IJEOMA F. UCHEGBU ET AL.: "Polymeric Chitosan-based Vesicles for Drug Delivery" JOURNAL OF PHARMACY AND PHARMACOLOGY, vol. 50, no. 5, 1 May 1998 (1998-05-01), pages 453-458, XP002125497 page 455 -page 457 --- -/--	1-31

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 December 1999	14/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lensen, H

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INTERNATIONAL SEARCH REPORT

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PCT/GB 99/02960

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 4 024 073 A (HIROHIKO SHIMIZU ET AL.) 17 May 1977 (1977-05-17) column 3, line 21 - line 39	1-31
Y	US 5 512 091 A (CAROL A. STEINER) 30 April 1996 (1996-04-30) column 1, line 40 - line 56	1-31
A	EP 0 798 335 A (HOECHST) 1 October 1997 (1997-10-01)	

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.nformation on patent family members

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